CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-819

MICROBIOLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products
Clinical Microbiology Consultation

Date Received by CDER: 21 December 2007
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Reviewer: Kerry Snow

APPLICANT

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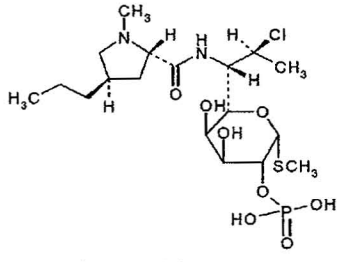
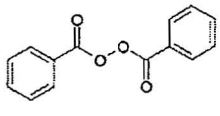
DRUG PRODUCT NAME b(4)

Proprietary name: ——
Code name: IDP-110
Drug name: clindamycin phosphate 1.2% and benzoyl peroxide 2.5%

Clincamycin phosphate:
Chemical name: methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxzmido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)
Molecular formula: $C_{18}H_{34}ClN_2O_8PS$
Molecular weight: 504.97
Chemical structure:



Benzoyl peroxide:
Chemical name: peroxide, dibenzoyl
Molecular formula: $C_{14}H_{10}O_4$
Molecular weight: 242.23
Chemical structure:



PROPOSED INDICATION

Topical treatment of acne vulgaris in patients 12 years or older

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT

Dosage form: clindamycin phosphate 1.2% and benzoyl peroxide 2.5% in an aqueous gel in 50 gram jars
Route of administration: topical
Dosage: applied to affected areas once daily or as directed by physician

DISPENSED

Rx

RELATED DOCUMENTS

NDA 050741: Duac Topical Gel (1% clindamycin and 5% benzoyl peroxide) (Stiefel Laboratories, Inc.)
NDA 050756: Benzaclin (1% clindamycin phosphate and 5% benzoyl peroxide) (Sanofi Aventis US)

REMARKS

The Division of Dermatology and Dental Products has requested a clinical microbiology consult for NDA 050819, —— (clindamycin phosphate 1.2%, benzoyl peroxide 2.5%). The proposed indication is for the treatment of acne vulgaris. The applicant submitted a 505(b)(2) application. There are no antimicrobial indications in the proposed label. b(4)

INTRODUCTION

Acne vulgaris is a common skin infection, most often seen in adolescents but occasionally continuing into adulthood. Over 85% of adolescents experience acne during their lifetimes [James 2005]. The pathogenesis of acne vulgaris is multifactorial, involving at least four processes, including 1) excess sebum production, 2) follicular hyperproliferation, 3) inflammation, and 4) the proliferation of *Propionibacterium acnes* [Collier 2008]. The association of P. acnes in the pathologic process is unclear, although studies point to a role in the initiation and/or exacerbation of the local inflammatory response [Leyden 1975].

In a report published in 2006 [Zaenglein 2006], an expert committee recommended combination therapy as the optimal management strategy for acne vulgaris. The rationale for this recommendation included the goal of addressing the multifactorial nature of the condition as well as the necessity for preventing antimicrobial resistance. Specifically, the group recommended a topical retinoid along with a topical antimicrobial as first-line treatment. In addition, benzoyl peroxide (BPO) was recommended (in addition to an antibiotic), in order to decrease the likelihood of resistance development. Topical antibiotics as monotherapy were not recommended.

Of the variety of antimicrobials with activity against *P. acnes*, the topical macrolides are most frequently used in first-line acne management, with clindamycin preparations marketed more frequently in the U.S. Topical clindamycin (1%) was approved for the treatment of acne in 1981, and is currently marketed as Clindagel (Galderma, NDA 050782), 1 % clindamycin in combination with 5% BPO is currently marketed as Benzaclin (Sanofi Aventis) and as Duac Topical Gel (Steifel Laboratories). Benzaclin was approved in December of 2000 under NDA 050756. Duac was approved in August of 2002 under NDA 050741.

Rare accounts have associated topical administration of clindamycin with the development of pseudomembranous colitis [Parry 1986]. Long-term topical administration of antibacterials has been associated with an increased rate of upper respiratory tract infections [Marolis 2005].

The current application (NDA 050819) is for a 2.5% BPO and 1% clindamycin (1.2% clindamycin phosphate) product. The Applicant has referenced safety and efficacy data submitted in support of an earlier application for a 5% BPO and 1% clindamycin product (——— . 1/5 gel). The Applicant proposes that the product described in the current application will provide comparable efficacy to ——— 1/5 (and other 1% clindamycin 5% BPO products), but will result in less irritation. The proposed label does not include an antibacterial claim. b(4)

MECHANISM OF ACTION

Clindamycin belongs to the lincosamide class of antimicrobials (along with lincomycin). The lincosamides suppress bacterial protein synthesis by binding to the 50S ribosomal subunit, interfering with peptidyl transferase activity. This mechanism (and the specific binding sites) are closely related to those described for the macrolides, streptogramins, and chloramphenicol [Murray 2007].

Benzoyl peroxide (BPO) may have broad-spectrum antibacterial activity related to its role as an oxidizing agent, although the specific mechanism of bacterial killing is not well described. The reportedly modest direct antimicrobial effect of BPO may be enhanced by its tendency to concentrate in lipid-rich partitions [Decker 1989]. In addition to its antibacterial activity, BPO is also active as a keratolytic and desquamative agent, both pertinent with regard to the treatment of acne vulgaris.

Recent studies have suggested a synergistic effect associated with the co-administration of topical macrolides and BPO [Burkhart 2000], purportedly the result of enhanced release of free radicals by BPO and the anti-inflammatory properties of the macrolides.

The applicant has submitted no data regarding the mechanism of action of either clindamycin or BPO.

SPECTRUM OF ACTIVITY

Clindamycin is active against most Gram positive organisms, except the enterococci. It is also active against most anaerobes, including *Bacteroides fragilis*. The lincosamides are inactive against aerobic Gram negative bacteria and against enterococci. b(4)

The applicant has presented summary data from a single study performed by '[redacted] designed to describe the in vitro activity of the 1% clindamycin and 2.5% BPO combination, in addition to its active monads. The investigators selected 86 isolates of *P. acnes*, collected from human sources from different geographical regions. Testing was performed using agar dilution techniques for anaerobic susceptibility determinations, approved by CLSI (M11-A5). Quality control organisms were run with each batch (*P. acnes* NCTC 737 and *P. granulosum* NCTC 11865).

The investigation included isolates with well-described phenotypes, including MLS-resistant and MLS-susceptible isolates. Three genotypes with mutations in genes encoding 23S RNA (2057, 2058, and 2059), one genotype with an *erm*[X] mutation (encoding a ribosomal methyltransferase), one genotype with a mutation in the 16S gene (1058, encoding resistance to tetracyclines), genotypes with multiple resistance mutations, and clindamycin-resistant isolates with unknown genotypes were tested. Resistant phenotypes were "confirmed" by disk diffusion testing, using clindamycin, erythromycin, and tetracycline.

The researchers found "no potentiation of activity" when BPO and clindamycin were combined in a ration of 2.5:1, and concluded that "those strains more susceptible to clindamycin were inhibited by the expected level of clindamycin in the combination and those resistant to clindamycin were inhibited by the expected level of benzoyl peroxide."

MECHANISM OF RESISTANCE

Resistance to clindamycin may be inherent or acquired. Gram negative bacteria are inherently resistant to the lincosamides, probably due to the hydrophobicity of the molecule and its inability to cross the bacterial outer membrane.

Acquired resistance involves one or a combination of mechnisms, including target modification, enzymatic deactivation, or active efflux. Resistance to the lincosamides is of the macrolide-lincosamide-streptogramin B (MLS_B) type and may be induced or constitutive [Bryskier 2005]. In staphylococcal species, constitutive resistance includes all classes of MLS_B antibiotics, while induced resistance does not result in lincosamide resistance. Studies of propionibacterial species have demonstrated four different patterns of MLS_B-type resistance [Eady 1989], including isolates that were constitutively resistant to all MLS antibiotics, isolates that were inducibly resistant to all MLS antibiotics, isolates that were inducible to MLS antibiotics excluding erythromycin, and isolates that were not classifiable.

A primary rationale for clindamycin-BPO combination therapy is to reduce the development of resistant isolates of *P. acnes* (and skin commensals).

In a 1994 report [Eady 1994], researchers used the checkerboard technique to investigate the interaction of erythromycin and 5 % BPO against isolates of *P. acnes*. The data showed indifference in the majority of isolates tested (35 of 40), although BPO was shown to inhibit all tested isolates, regardless of erythromycin MIC. The researchers concluded that this suggested a role for the combination in discouraging macrolide resistance.

A 1992 study [Harkaway 1992] demonstrated the effect of combination erythromycin-5% BPO therapy in decreasing the number of erythromycin-resistant *Staphylococcus epidermidis* isolates after 12 weeks of treatment.

In a 1996 report (Eady 1996], reported the results of two clinical trials designed to investigate the ability of a 5% BPO and 3% w/w erythromycin preparation in preventing the selection of resistant isolates of *P. acnes* during therapy, and in inhibiting the growth of baseline erythromycin-resistant isolates. The investigators demonstrated that the combination therapy reduced both the total number of propionicabacteria and the number of erythromycin-resistant isolates more than treatment with erythromycin alone.

Leyden, et al, demonstrated similar reductions in total numbers of facial propionibacteria and a decrease in resistant isolates following treatment with a 5% BPO and 1% clindamycin gel, compared to topical clindamycin alone (in gel, lotion, and solution forms) [Leyden 2001]. The investigators showed that clindamycin resistance appeared to increase after 12 weeks of treatment in patients receiving only the topical antibiotic.

This reviewer was unable to find published data that demonstrated decreased development of resistance in isolates of *P. acnes* exposed to an antibiotic (macrolides or clindamycin at any concentration) and BPO in concentrations less than 5% (e.g. 2.5% BPO). No data is available describing the development of resistance to BPO alone, at any concentration. The Applicant has performed no mechanism of resistance studies and has presented no data describing the development of resistance in P. acnes to the proposed combination product.

CLINICAL TRIALS

The Applicant has submitted data from one Phase II clinical trial and two identical Phase III clinical trials:

> Phase 2 Trial: DPS-07-12-2005-002 A Phase II, Multi-center, Randomized, Evaluator-Blind, Vehicle-Controlled, 6-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clinaben (1/2.5), Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in The Treatment of Acne Vulgaris
>
> Phase 3 Trial: DPSI-06-22-2006-012 A Phase III, Multi-center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clinaben (1/2.5) Gel, [redacted] Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in The Treatment of Moderate to Severe Acne Vulgaris b(4)
>
> Phase 3 Trial: DPSI-06-22-2006-017 A Phase III, Multi-center, Randomized, Double-Blind, Vehicle-Controlled, 4-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of Clinaben (1/2.5) Gel, [redacted] Vehicle, Clindamycin (1%), and Benzoyl Peroxide (2.5%) Gels in The Treatment of Moderate to Severe Acne Vulgaris (4)

Males and females 12 years of age and older (multiple ethnicities) were enrolled in the Phase II study. Subjects were graded according to the "Evaluator's Global Severity Score" (or "Evaluators Global Assessment" (EGA))., with "moderate to severe acne vulgaris" serving as the primary inclusion criterium. Dosing was once or twice daily for 12 weeks. Investigators intended to evaluate the safety and efficacy of IDP-110 Gel. The 6 treatment groups included: IDP-110 Gel q.d.; clindamycin gel 1% q.d.; BPO get 2.5% q.d.; IDP-110 vehicle gel q.d.; IDP-110 Gel b.i.d.; and BPO gel 2.5% b.i.d. Evaluated endpoints included a comparison of treatment to vehicle for clinical improvement, a comparison of time courses to clinical resolution or improvement, a comparison of once vs. twice daily dosing

for efficacy and tolerability, and a comparison of proportions of subjects with an EGA score of clear or almost clear at specific timepoints. Baseline inflammatory lesions were similar in all 6 treatment groups, and results were similar between PP and ITT populations. Fewer mean inflammatory lesions were seen at all time points (weeks 4, 8, 10, and 12) in the IDP-110 q.d. treatment arm, followed by the IDP-110 b.i.d. treatment arm.

Males and females between the ages of 12 and 70 (multiple ethnicities) were enrolled in the two, identical Phase III studies. Primary efficacy variables included an absolute change from baseline to Week 12 in inflammatory lesion counts, and percent of subjects who achieved a two-point reduction at Week 12 in the EGA.

Study DPSI-06-22-2006-012 enrolled 1414 subjects at 35 sites. The investigators reported statistically significant differences between IDP-110 gel treatment and clindamycin gel ($p = 0.002$), and IDP-110 gel treatment and BPO gel treatment ($p = 0.001$), with IDP-110 being more clinically effective in both cases.

Study DPSI-06-22-2006-017 enrolled 1399 subjects at 33 sites. The investigators reported statistically significant differences between IDP-110 gel and either monad (clindamycin gel, $p = 0.009$; BPO gel, $p = 0.009$), and between IDP-110 gel and vehicle ($p < 0.001$).

There were no microbiologic endpoints in any clinical trial conducted to support this application, and no studies conducted to determine the role of the combination therapy in preventing or reducing antimicrobial resistance to the combination or either monad, in species defined as pathogens associated with acne vulgaris (e.g. *Propionibacterium acnes*) or in skin commensals and potential skin pathogens (e.g. *Staphylococcus aureus*).

CONCLUSIONS

b(4)

The proposed label for ——— ———, Gel (clindamycin phosphate 1.2% and benzoyl peroxide 2.5%) contains no microbiologic indication. The microbiology portion of the proposed label states:

> "Clindamycin and benzoyl peroxide individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against P. acnes is not known and was not examined in clinical trials with ——— ——— Gel.
>
> P. acnes resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin.

b(4)

This reviewer recommends no changes to the proposed label. From a clinical microbiology perspective, the Application is approvable.

Of concern, though, is the understanding (articulated in this application) that topical administration of clindamycin results in increased resistance to various antimicrobials (including the macrolides), and that this effect may have serious implications, including the disruption of gut and respiratory flora with overgrowth of pathogens. Several recent studies have suggested that topical administration of BPO alone may be as efficacious as existing topical combinations. Resistance to BPO is currently unknown, and the potential for such resistance appears low. These two factors suggest that additional data would be useful in determining the risks and benefits of topical antimicrobial administration, and that combination products with a reduced concentration of BPO be analyzed for their relative ability to inhibit resistance.

With these concerns in mind, this reviewer suggests that the Applicant provide additional information regarding the ability of the proposed concentration of BPO (2.5%) to inhibit the development of resistance to clindamycin in relevant species including *Propionibacterium acnes* and other skin commensals. This information may be submitted by reference to recent literature or by post-marketing studies conducted by the Applicant.

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Fred Marsik/MicroTL/HFD-520
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